PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Torsten ALMEN, et al.

Appln. No.: 10/552,069

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Group Art Unit: 1796

Examiner: Angela C SCOTT

For: BONE CEMENT COMPOSITIONS

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Bjarne Brudeli, hereby declare and state:

I am a citizen of Norway;

I have received the degree of Master in Pharmacy in 2002 from School of Pharmacy, University of Oslo;

I have been employed by IoPharma Technologies AB since February 2007, where I hold a position as Director of Research, with responsibility for research and development in IoPharma Technologies AB.

I am one of the inventors of the present application and am familiar with the subject matter being claimed as well as with the Office Action dated October 12, 2010.

In order to demonstrate the unexpectedly superior results provided by the present invention and the patentability of the present claims over Lidgren (US 6,586,009) and the cited

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secondary references, the following additional experiments were conducted by me or under my supervision and control.

Lidgren describes a composition with a particulate component comprising separate particles of water soluble non-ionic organoiodine compound and polymer. Lidgren's composition does not contain a dissolved organoiodine compound. As explained in the second paragraph at page 2 of the present application, agents such as iohexol and iodixanol, the preferred contrast agents of Lidgren, are known to have a negative impact on the mechanical properties of cements into which they are incorporated.

In contrast, the present invention provides an radio-opaque bone cement with unexpectedly superior mechanical strength by using dissolved organoiodine compounds. The following experiments were conducted to compare bone cements as described in Lidgren with the cements according to the present invention and the results show how the distinguishing features contribute to solving the problem and that the claimed invention therefore has an inventive step.

Experimental

There is no evidence that the Examples of Lidgren were ever carried out and no results are reported with which to compare the cements of the present invention. It was therefore necessary to prepare cements with contrast agents according to Lidgren and compare their mechanical properties to those of the present invention.

Three groups of bone cements were prepared, one group containing iohexol hexaacetate (IHA, a contrast agent soluble in the cement according to the present invention) and further sets

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of cements containing iohexol (IHX) and iodixanol (IDX). IHX and IDX are contrast agents as suggested by Lidgren and are not soluble in bone cement, they therefore must be incorporated in the form of insoluble particles. The IHA cements, on the other hand, comprise IHA dissolved in one of the portions of the cement as required by claim 1. The experiments are therefore intended to demonstrate how the distinguishing feature of the present invention (the dissolved contrast agent) contributes to solving the problem of impaired mechanical properties.

The IHX bone cement was prepared by volumetrically mixing 36.8 g of "Palacos® R" polymer (a product based on methacrylate co-polymers) powder with 3.2 g IHX (giving a concentration of the contrast media of 8 wt% or 3.71 wt% iodine), and later mixing it with 20 mL of Palacos® R monomer liquid.

The IDX bone cement was prepared by volumetrically mixing 34.5 g of Palacos® R polymer powder with 5.5 g IDX (giving a concentration of the contrast media of 13.75 wt% or 6.75 wt% iodine), and later mixing it with 20 mL of Palacos® R monomer liquid.

The IHA bone cement was prepared by mixing a PMMA co-polymer powder (with 20 wt% IHA, which corresponds to 7.09 wt% iodine) already incorporated in the particles, with 20 mL of Palacos® R monomer liquid.

In each case the bone cement materials were prepared by mixing the pre-polymerized copolymeric powder with the monomer liquid in an Optivac vacuum-mixing system (Biomet Europe, Sjöbo, Sweden). Three minutes after mixing, the cement was injected into moulds in order to produce half-size ISO 527 specimens, and then put under pressure. After curing, the specimens were removed from the mould and stored in saline solution at 37±1°C for a minimum

of two weeks as a simulated ageing procedure. Prior to testing, the cross sectional area of the gauge section was measured. Testing was performed on an Instron 8511 load frame (High Wycombe, UK) with an MTS TestStar II controller (Minneapolis, USA). Strain was measured using an Instron 2620-602 extensometer (High Wycombe, UK), and the specimens were loaded under displacement control at 2 mm min^{-1}. The fracture surfaces were inspected and those specimens that contained pores with a diameter of more than 1 mm were excluded. Maximum tensile strength and strain at failure were recorded and the results are shown in the following Figures 1 to 4 .

Discussion

The bone cements containing 20% IHA show significantly higher tensile strength than the IHX cement ($p<0.001$), see Figure 1. Moreover, the strain at failure is significantly higher for the IHA cements when compared to the IHX cements ($p<0.00001$), see Figure 2.

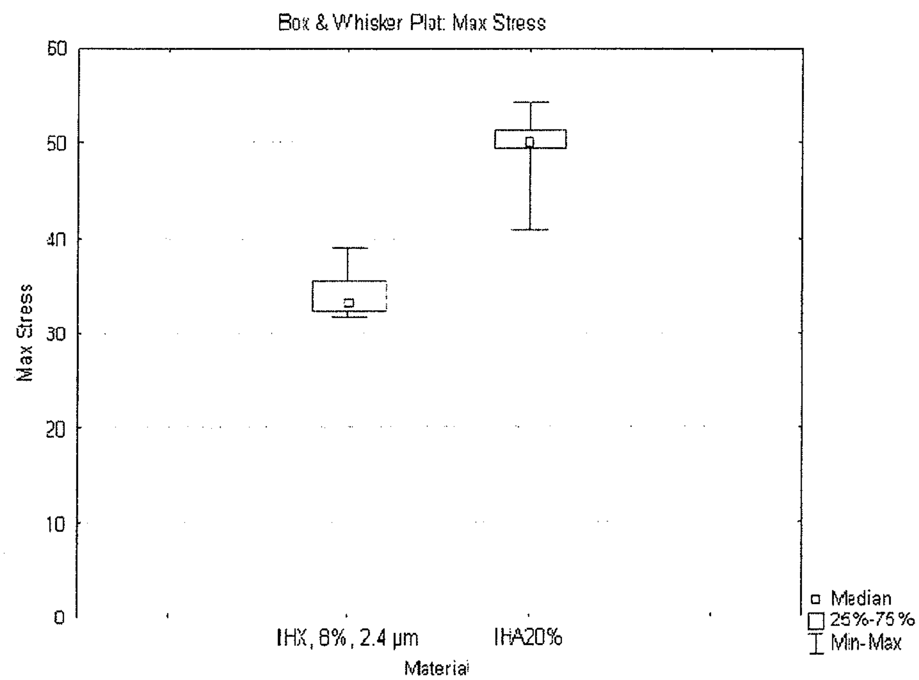

Figure 1 Maximum tensile strengths for the iohexol and iohexol hexaacetate bone cements

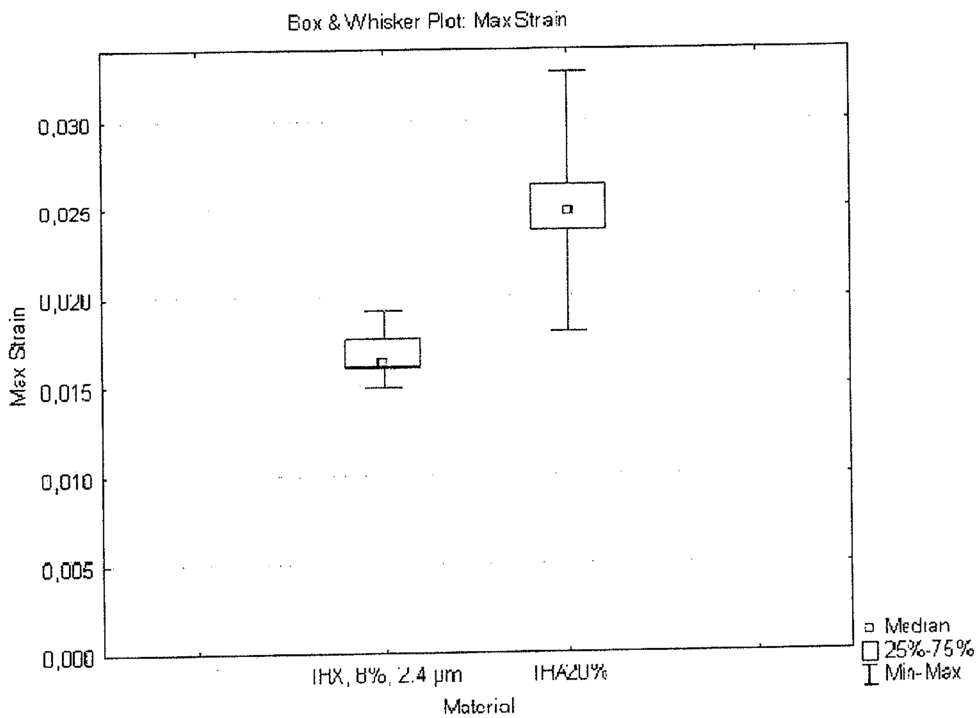

Figure 2 Ultimate tensile strain for the iohexol and iohexol hexaacetate bone cements.

The bone cements containing 20% IHA also show significantly higher tensile strength than the bone cements containing 13.75% IDX ($p<0.000001$), see Figure 3. The strain at failure is also significantly higher for the IHA cement than for the IDX cement ($p<0.02$), see Figure 4. The IHA cement showed a 27 % higher maximum tensile strength than the IDX cement, and a 16 % higher strain at failure.

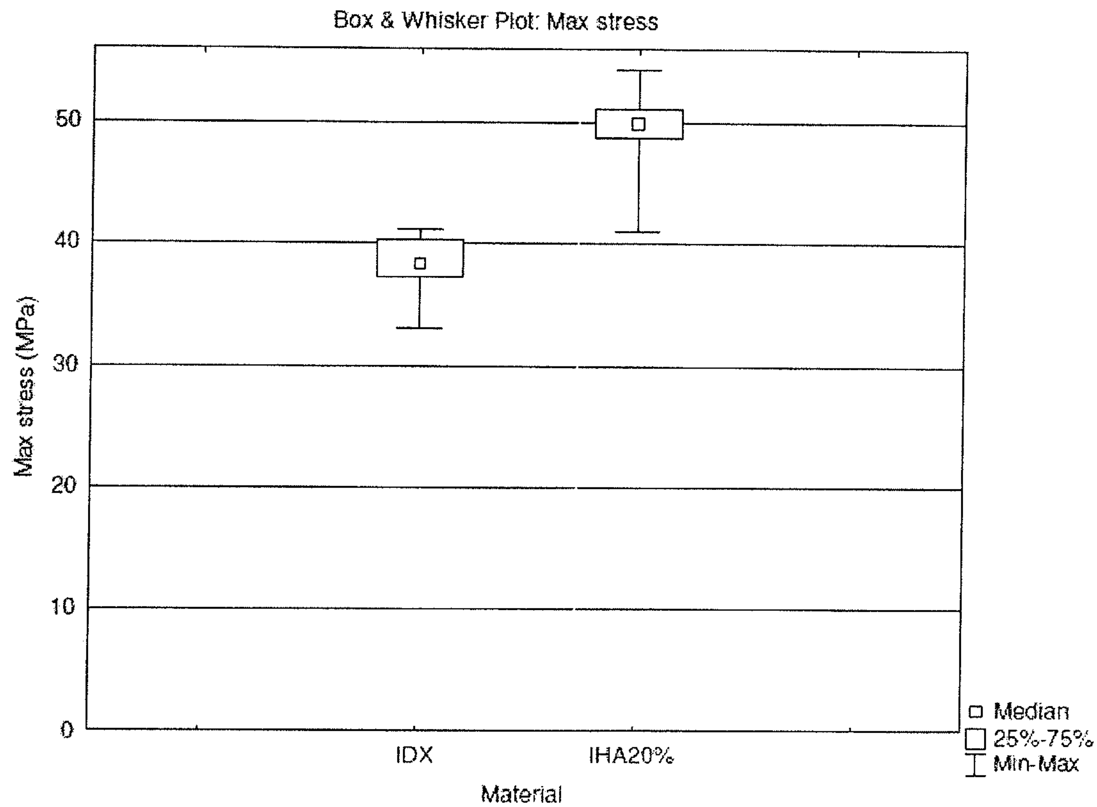

Figure 3 Maximum tensile strengths for the iodixanol and iohexol hexaacetate bone cements.

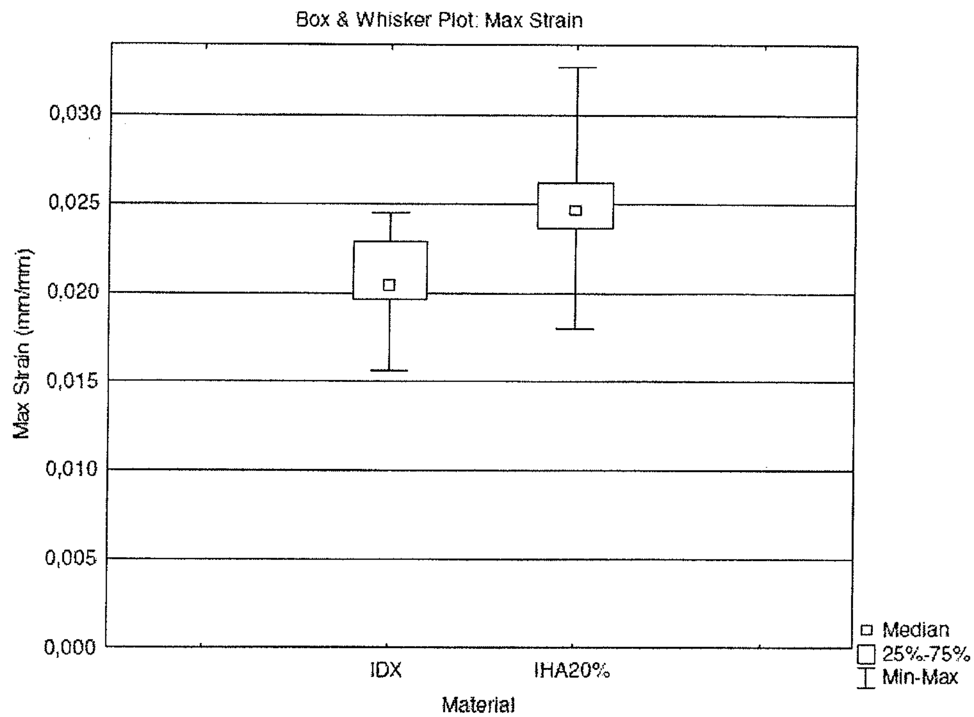

Figure 4 Ultimate tensile strain for the iodixanol and iohexol hexaacetate bone cements.

The IHA cements which contain a dissolved organoiodine compound therefore have improved mechanical properties over the cements suggested by Lidgren which contain particulate organoiodine compounds.

The three types of cement are summarized in the following table:

Contrast agent	**Concentration of contrast agent in cement* (wt%)**	**Concentration of iodine in cement* (wt%)**
IHX, Iohexol	8	3.71
IDX, Iodixanol	13.75	6.75
IHA, Iohexol hexaacetate	20	7.09

*Prior to addition of 20mL of Palacos®R monomer liquid.

The table shows the concentration of contrast agent and iodine in each composition before addition of the equal amounts of monomer (20 mL of Palacos® R monomer liquid). The experiment was designed such that cements with comparable amounts of iodine were used. Although the IHA cements had slightly more iodine than the IHX and IDX cements, this meant that the IHA cements attenuate more X-rays and so were tested under a disadvantage, making the setup into somewhat of a worst case scenario for the IHA cements. Furthermore, as addition of contrast agent is known to weaken the resulting cement, the IHA compositions would be expected to perform worst in the strength tests due to their higher contrast agent content. The results therefore show a surprising and significant improvement when the dissolved contrast agents according to the present invention are used.

Conclusions

In summary, bone cement containing IHA shows significantly superior mechanical properties than bone cements containing IHX or IDX, even at higher contrast media contents.

The present invention relates to monomer/polymer soluble iodinated X-ray contrast agents in bone cement where the contrast agent is dissolved in the cement. Incorporation of the contrast agent into the monomer and/or polymer portion of the cement reduces the negative

influence (reduction of mechanical strength and increased risk of loosening) of the contrast agent in the final bone cement. Because the organoiodine compound is dissolved in one of the portions, the bone cement has increased mechanical strength as shown by the above experiments. Incorporation of a dissolved contrast agent into the monomer and/or polymer portion is neither taught nor suggested by the prior art, therefore the claims are patentable over the prior art.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 8th of February 2011

Bjarne Brudeli